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EXAMINER	
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ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/922,718	NIELSEN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 May 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-69* is/are pending in the application.

4a) Of the above claim(s) *2-4,6-11,13-15,23-27,31 and 40-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 5, 12, 16-22, 28-30, 32-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/7/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. The response received May 12, 2003 to the restriction requirement of Marc 11, 2003 is acknowledged and has been entered. Upon review and reconsideration, the previous restriction requirement is vacated.

2. Claims 1-69 are pending in the application and are currently under prosecution.

3. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Groups 1-96. Claims 1-9 are drawn to a method for better understanding at least one of four variables drawn to tumors by determining the level of four markers, classified in Class 435, subclasses 4, 7.1. It is noted that the number of groups have been determined by Factorial analysis wherein the at least one of four variables equals 4! which equals 24 and whereby determining the level of each marker for each of the groups is considered a distinct invention, thus 4 times 24 equals 96 groups. Applicant is required to elect a single invention, that is, a single marker and one or more specifically identified variables for examination. It is noted for Applicant's convenience that this is a requirement for the election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn to multiple methods using multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the Markush group, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int.

1984). Since the members of the groups do not share a substantial structural feature disclosed as being essential to utility of the Markush group, the groups as claimed fail the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEP 803.02. Claims 1-9, 15, 17-18, 20-21, 23-24, 27-33, 35, 36-38 40-46, 49-51, 53, 55-69 will be examined as they are drawn to the elected invention.

Itt is noted that in addition to the 96 distinct groups claimed in claim 1 as disclosed above, the 96 inventions of claim 1 have been determined to linking inventions drawn to tumor type. Thus applicant is required to elect a single invention from the 96 inventions set forth above and upon election of said invention to elect a linked tumor type group from those set forth below.

In particular, the restriction requirement among the linked inventions is subject to the nonallowance of the elected linking claim(s), claim 1 and 36 (if drawn to the elected invention) wherein inventions 97-109 are linked by said claims. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01. Upon election of a

single group as required above, Applicant must elect a single group from those set forth below.

Group 97. Wherein claims are drawn to a method as elected above for better understanding breast tumor, classified in Class 435, subclasses 4, 7.1.

Group 98. Wherein claims are drawn to a method as elected above for better understanding gastric tumor, classified in Class 435, subclasses 4, 7.1.

Group 99. Wherein claims are drawn to a method as elected above for the better understanding of colon tumor, classified in Class 435, subclasses 4, 7.1.

Group 100. Wherein claims are drawn to a method as elected above for better understanding of lung tumor, classified in Class 435, subclasses 4, 7.1.

Group 101. Wherein claims are drawn to a method as elected above for the better understanding of ovarian tumor, classified in Class 435, subclasses 4, 7.1.

Group 102. Wherein claims are drawn to a method as elected above for the better understanding of pancreatic tumor, classified in Class 435, subclasses 4, 7.1.

Group 103. Wherein claims are drawn to a method as elected above for the better understanding of urinary tract tumor, classified in Class 435, subclasses 4, 7.1.

Group 104. Wherein claims are drawn to a method as elected above for the better understanding of colorectal tumor, classified in Class 435, subclasses 4, 7.1.

Group 105. Wherein claims are drawn to a method as elected above for the better understanding of gynecological carcinomas other than ovarian as contemplated in the specification, classified in Class 435, subclasses 4, 7.1.

Group 106. Wherein claims are drawn to a method as elected above for the better understanding of brain tumors, classified in Class 435, subclasses 4, 7.1.

Group 107. Wherein claims are drawn to a method as elected above for the better understanding of sarcomas, classified in Class 435, subclasses 4, 7.1.

Group 108. Wherein claims are drawn to a method as elected above for the better understanding of haematological malignancy, classified in Class 435, subclasses 4, 7.1.

Group 109. Wherein claims are drawn to a method as elected above for the better understanding of skin cancers, classified in Class 435, subclasses 4, 7.1.

Group 110. Claims 36-38 are drawn to a method of detecting the presence of a malignant tumor comprising assaying PAI-1 DNA abundance, classified in Class 435, subclass 6.

4. **Groups 111-115.** Claims 36-39, 45 are drawn to a method for detecting the presence/determining progression of a malignant tumor comprising detecting one or more of PAI-1 DNA abundance, RNA abundance and protein abundance classified in Class 435, subclasses 4, 6, 7.1. It is noted that the number of groups have been determined by Factorial analysis wherein the combination of molecules to be assayed is drawn to 3 types of molecules to be assayed, 3! which equals 6 inventions. However, in point of fact, this group contains only 5 inventions

because the invention of assaying only PAI-1 protein abundance for determining progression of a malignant tumor has been joined to, and will be examined with, the inventions of claim 1 since this invention is also recited in claim 1. Applicant is required to elect and identify a single invention, that is, a single molecule or combination thereof to be assayed for examination. It is noted for Applicant's convenience that this is a requirement for the election of a Group for examination NOT a requirement for an election of species because although the claims are presented in Markush format, the claims are drawn to multiple methods using multiple agents which do not share, as a whole, a substantial structural feature disclosed as being essential to their utility. Thus, the analysis of the claims, for restriction purposes, is subject to the findings of the court wherein the court found that unity of invention exists where entities included within a Markush group share a substantial structural feature disclosed as being essential to utility of the Markush group, In re Harnisch, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). Since the members of the groups do not share a substantial structural feature disclosed as being essential to utility of the Markush group, the groups as claimed fail the Harnisch test and the claims are not accorded Markush restriction practice because they do not meet the requirements to be accorded Markush practice under MPEP 803.02. 5. The inventions are distinct, each from the other because of the following reasons:

Inventions 1-115 are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. For example, the groups are drawn to assaying different combinations of variables and markers wherein the markers are drawn to molecules with different structures and functions wherein tissues with different

pathologies and etiologies are assayed wherein the claims are drawn to a total of 115 distinct inventions wherein search and examination of all of the groups would require a high burden of search and represent an undue burden on Examiner.

Further, inventions 1-115 are related as combination and subcombination. Inventions in this relationship are distinct if it can be shown that (1) the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination and (2) that the subcombination has utility by itself or in other combinations (MPEP э 806.05(c)). In the instant case, the patentability of the combination does not rely necessarily and solely on the patentability of any one subcombination as clearly evidenced by the plural subcombinations claimed. Further, each of the subcombinations has utility by itself because each of the subcombinations are useful for screening for different parameters. Thus the claims are distinct as required by MPEP 806.05(c).

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. Groups 111-115 are further subject to election of a single disclosed species..

Claim 36 is generic to a plurality of disclosed patentably distinct species comprising assays of tumor types with different etiology and pathology with different materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success wherein the species are (a) mammary carcinomas, urological carcinomas, gynaecological acarcinomas, non-small cell lung tumors,

gastrointestinal cancers, brain tumors, sarcomas, haematological malignancy and skin cancers, all of claim 39.

8. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. In a telephone interview with Iver Cooper on September 19, 2006, Examiner requested that Mr. Cooper make an election, by telephone for the newly imposed restriction requirement. Mr. Cooper re-elected the group previously elected, that is, Mr. Cooper elected a method for determining the likelihood of progression of a malignant colon cancer in a subject comprising measuring PAI-1 abundance in a sample, using an immunoassay wherein two time points are compared – for the determination, with traverse. Thus, claims 2-4, 6-11, 13-15, 23-27, 31, 40-69 have been withdrawn from consideration by Examiner as being drawn to non-elected

inventions and Claims 1, 5, 12, 16-22, 28-30, 32-39 have been elected for and are under prosecution.

11. Applicant is advised that the response to this requirement to be complete must include confirmation of this election.

12. Some of Applicant's arguments drawn to the previous restriction requirement are relevant to the instant restriction requirement.

Applicant argues that the restriction requirement, now to 115 groups, would be inequitable given that Applicant would be required to file now 115 applications and further argues that examination of all of the inventions would not be an undue burden on the examiner. The argument has been considered but has not been found persuasive as Applicant is entitled to examination of only one invention and for the reasons set forth above examination of all of the groups would be an undue burden on Examiner.

Applicant argues that, as drawn to Groups 1-96 that there is a very close relationship among the four variables and while not identical they may be highly correlated. The argument has been considered but has not been found persuasive because, although the subject matter of the variables might be overlapping, the subject matter is not coextensive and the search and examination of all the groups would be an undue burden on Examiner.

Specification

13. The specification on page 1 should be amended to reflect the status of the parent applications.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise,

and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1, 5, 12, 16-22, 28-30, 32-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for screening for the likely progression of a malignant colon tumor in a tumor tissue/fluid sample by assaying for PAI-1 protein abundance.

The specification teaches that measurements of PAI-1 protein abundance in tumor tissue may be useful in predicting the progression of a known malignant tumor (see abstract). The specification further teaches that Ganesh et al. (1994 Cancer Res. 54, 4065-4071, IDS item) studied the prognostic impact of PAI-1 in 92 primary colon carcinoma samples and found no significant correlation between primary tumor PAI-1 as determined by sandwich ELISA, and patient outcome (para 0039 of the published application). In addition, the specification teaches that in a recent study performed at the Finsen Laboratory (unpublished), PAI-1 protein content was investigated. When comparing tumour PAI-1 levels with clinical outcome in the relative low number of patients, a trend towards statistical significance in survival between high versus low PAI-1 was seen (see Figure 6 and para 0040 of the published application).

The specification teaches that the prognostic value of plasma PAI-1 in patients with colorectal cancer was assessed by ELISA wherein patients were

randomly divided into two groups, the first group were used to search for an optimum cut-off value to separate patients into two groups with different survival. This optimized cut-off point was then tested in a second group of patients (p. 37, lines 24-30) wherein it was found that patients with plasma PAI-1 levels above the cut-off point had a 50% higher risk of death than patients with plasma PAI-1 levels below the cut-off point (p. 38, lines 1-7). Finally, the specification teaches that the study of the prognostic value of preoperative plasma PAI-1 in patients undergoing surgical resection for colorectal cancer suggests that high plasma levels of PAI-1 are associated with short overall survival.

As drawn to solid tumor tissue assays, one cannot extrapolate the teaching of the specification to the enablement of the claims because the art recognizes that there is no significant correlation between primary tumor PAI-1 protein abundance and patient outcome. In particular, Ganesh et al specifically dismiss the involvement of PAI-1 protein abundance as a prognostic marker for clinical outcome of colon cancer because there was no correlation found between PAI-1 protein abundance and clinical outcome. Given that there is no correlation found between PAI-1 protein abundance and clinical outcome, it does not appear that PAI-1 protein concentration as assessed in primary colon cancer tissue is in any way associated with the likely progression of a malignant tumor in a subject. Although the specification teaches that when comparing tumour PAI-1 levels with clinical outcome in a relative low number of patients, a trend towards statistical significance in survival between high versus low PAI-1 was seen, it is clear from the information in Figure 6 that it is more likely than not that the differences in survival between high and low PAI-1 abundance patients is due to normal variability and is not in fact associated with an ability to use PAI-1 protein

abundance in primary colon cancer tissue to screen for the likely progression of a malignant tumor. This is especially true given the teachings of Ganesh et al that clearly demonstrate a lack of correlation between PAI-1 protein abundance in primary tumor tissue and clinical outcome. Thus one would not expect to be able to screen for likely colon cancer progression with the claimed assay.

As drawn to body fluid assays, one cannot extrapolate the teaching of the specification to the enablement of the claims because the art recognizes that high body fluid PAI-1 levels are not limited to patients presenting only with colon cancer. In particular, Lin et al, (IADR/AADR/CADR 83rd General Session, March 10, 2005, Seq No. 130), specifically teach that patients with alveolar bone loss, that is periodontal disease as well as coronary artery disease were found to have elevated serum PAI-1 levels. The reference specifically teaches that "these data suggest that a link between periodontitis and atherosclerotic events is an increase in serum PAI-1 levels." Further, Yki-Jarvinen et al (Arterioscler Throm Basc Biol., 2003, 23:688-694) specifically teach that in obese subjects, PAI-1 levels are elevated in plasma (p. 689, col 1). Given that a subset of the population of the United States is obese, given that periodontal disease is rampant, given that a subset of the population suffers from atherosclerosis, given that elevated body fluid levels of PAI-1 are found in multiple conditions, it would be expected that at least a large subset of patients with colon cancer would also present with these conditions and would also present with high body fluid PAI-1 levels, regardless of whether that level was associated with likelihood of proession of colon cancer. However, although claim 1 requires that the level of PAI-1 protein abundance be correlated to a corresponding reference sample and claim 36 requires that the difference in levels be correlated with an established level of difference which is

indicative of a high likelihood of tumor metastasis, that is progression, the specificiation does not teach what that corresponding reference sample/sample indicative of a high likelihood of tumor metastasis should be or where to determine that reference amount or how to predictably distinguish between a patient with likely colon cancer progression and ones that have elevated PAI-1 protein abundance due to obesity, artherosclerosis or periodontal disease.

The specification provides insufficient guidance with regard to this issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

16. If Applicant were able to overcome the rejections set forth above, Claim 1, 5, 12, 16, 20-22, 28-30, 32-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for the likely progression of a malignant colon tumor by assaying for PAI-1 protein abundance in a preoperative fluid/plasma sample with wherein patients that present with PAI-1 protein abundance at or above 0.58 ng/mg protein have tumors that will likely progress, does not reasonably provide enablement for a method for screening for the likely progression of a colon cancer in a fluid/plasma sample or screening by assaying at a first point in time and at a second point in time. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for screening for the likely progression of a colon cancer in a fluid/plasma sample. This means screening with any cut-off point, screening at any disease point or combination of points.

The specification teaches that the prognostic value of plasma PAI-1 in patients with colorectal cancer was assessed by ELISA wherein patients were randomly divided into two groups, the first group were used to search for an optimum cut-off value to separate patients into two groups with different survival. This optimized cut-off point was then tested in a second group of patients (p. 37, lines 24-30) wherein it was found that patients with plasma PAI-1 levels above the 0.58ng/mg PAI-1 protein had a 50% higher risk of death than patients with plasma PAI-1 levels below the cut-off point (p. 38, lines 1-7). Finally, the specification teaches that the study of the prognostic value of preoperative plasma PAI-1 in patients undergoing surgical resection for colorectal cancer suggests that high plasma levels of PAI-1 are associated with short overall survival.

The specification further teaches that it has recently been observed that in patients with advanced colon adenocarcinomas (Dukes D) plasma PAI-1 levels are correlated with tumour burden, e.g. high plasma PAI-1 level before debulking surgery, significant fall postoperatively and then steady increase during disease progression (para 0055 of the published application).

One cannot extrapolate the teaching of the specification to the scope of the claims because (1) the art recognizes the critical nature of cut-off points for accurate assessment of assays related to disease and (2) the specification teaches that plasma PAI-1 protein abundance levels varies with debulking of tumor.

(1) As set forth above, the art teaches that patients with obesity, arterosclerosis and periodontal disease present with elevated levels of PAI-1

protein abundance in body fluids. Further, As set forth above, the specification teaches that the exemplified body fluid/plasma assay was predictive of differential survival/likely progression of disease when a cut-off point of 0.58 ng/mg protein, which separated patients into two groups with different survival. Applicant recognizes the critical nature of cut-off points to predictably screen for likelihood of cancer progression wherein, as set forth above, the specification teaches that measuring PAI-1 protein abundance may be useful in predicting the progression of a known malignant tumor. In particular, as drawn to colon cancer the specification teaches at paragraph 0184 of the published application that "Measurement of plasma PAI-1 might then be used to divide colorectal cancer patients into groups of low versus high risk of recurrence. Only patients at high risk of recurrence/progression of disease should then be offered adjuvant systemic chemotherapy". Given the teaching of the specification wherein it is specifically contemplated that only patients at high risk of recurrence/progression of disease should be offered adjuvant systemic chemotherapy, the criticality of the cut-off point is clear. In addition as drawn specifically to claim 28 which claims that the method determines whether the subject has at least a 50% higher risk of death, it cannot be predicted, nor would it be expected that any cut-off point other than 0.58 ng/mg protein would function to predictably identify a subject that has at least a 50% higher risk of death.

Further, not only the specification but also the art recognizes the critical nature of cut-off points. In particular, Stites et al (Basic and Clinical Immunology, 7th Ed, Appleton and Lange, Norwalk, 1991, page 260) specifically teaches that when any test is used to make a decision (for example of whether to offer adjuvant systemic chemotherapy), there is some probability of drawing an erroneous

conclusion and that predictive value theory can be used to deal with this problem. The reference further teaches that sensitivity is defined as the fraction of diseased subjects with abnormal test results and that specificity is defined as the fraction of nondiseased subjects who have a normal laboratory test. Further, Stites et al teach that the positive predictive value is the fraction of abnormal tests that represent disease and the negative predictive value is the fraction of normal tests that represent the absence of disease (p. 260, col 1). Stites et al specifically teach that sensitivity and specificity reveal something about the test *given prior knowledge about the disease status* (emphasis in the original document), whereas positive and negative predictive values *estimate the likelihood of disease given the test result* (emphasis in the original document). Clearly it is the latter case that is of interest when trying to make a determinination (p. 260, para bridging cols 1 and 2). The difficulty with the determination of the positive predictive value for the claimed assay, is that neither the claims nor the specification provide guidance on a cut-off value other than 0.58 ng/ml PAI-1 protein abundance in body fluid. Although the specification discloses that this is the optimized figure, it is not possible to predict from the teaching of the specification or the art of record what other cut-off figure would function as claimed, that is to establish the likelihood of colon cancer progression so that only patients at high risk could be offered adjuvant systemic chemotherapy, sparing those patients at low risk as contemplated in the specification with a reasonable expectation that the patients will be appropriately treated.

(2) As drawn to the time of assay, as set forth above, the specification teaches that preoperative body fluid sample is useful for screening for likelihood of colon cancer progression. The specification further teaches that it has been

established that plasma PAI-1 levels are correlated with tumour burden, e.g. high plasma PAI-1 level before debulking surgery, significant fall postoperatively and then steady increase during disease progression. Thus, it is not clear and certainly could not be predicted that assay of a sample, for example, post operatively would be useful for the claimed method because the specification clearly teaches that the level of PAI-1 falls after debulking and only increases with disease progression. Given that the level of PAI-1 would apparently be low after debulking, it could not be predicted that the PAI-1 protein abundance in debulked patients would be different from that in patients whose cancer is not likely to progress or that these patients could be predictably distinguished. Further, it is not clear how assaying a sample, wherein the sample is taken after debulking and has increased PAI-1 protein abundance could be used to screen for likely progression of disease because applicant clearly states that increases in PAI-1 protein abundance found in patients after debulking is found with disease progression. Since it is found with disease progression, this parameter is not predictive of likely progession because disease is already in the progress of progressing. Clearly, as drawn to the claims claiming two step processes wherein the sample is taken at a single time point and at a later time point, it would not be expected, nor could it be predicted that the two point assay system would be predictive of a likelihood of progression for the reasons set forth above.

The specification provides insufficient guidance with regard to this issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable

expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

17. The specification is objected to and claim 30, 32-33 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claims are drawn to HT-1080 fibrosarcoma cells, antibody secreted by clone 2, antibody secreted by clone 4.

It is unclear if cell lines which produce antibodies having the exact structural and chemical identity of monoclonal antibodies secreted by the hybridomas of clone 4 and HT-1080 fibrosarcoma cells are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell lines producing monoclonal antibodies of clones 2 and 4 and HT-1080 fibrosarcoma cells, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also

occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, secreted by clones 2 and 4. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of HT-1080 fibrosarcoma cells. Further, although Applicant has disclosed the deposit of clone 1, this is an insufficient assurance that the deposit has been made and all the conditions of MPEP 608.01 (p)(c) met.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

18. Claims 1, 5, 12, 16-22, 28-30, 32-34, 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30, 32-33 are indefinite because claim 30 recites the phrase "human HT-1080 fibrosarcoma cells" as the only means of identifying the cell line. The use of laboratory designations only to identify a particular cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct cell lines. Amendment of the claims to include the depository accession number of the cell line is required, because deposit accession numbers are unique identifiers which unambiguously define a cell line.

Claims 32-33 are indefinite in the recitation of the phrases "clone 2" and "clone 4", respectively. The claims are confusing because it is not clear what is meant by the claimed clones. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the cell line is required, because deposit accession numbers are unique identifiers which unambiguously define a cell line.

Claims 36-39 are indefinite because claim 33 recites the phrase "a high likelihood". The phrase "high likelihood" is a relative phrase which renders the claim indefinite. The term is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 1, 5, 12, 16-22, 28-30, 32-34, 36-39 are rejected under 35 U.S.C. § 112, second paragraph, because claim 1 requires a "corresponding reference" and claim 36 requires an established level of difference that is indicative of a high likelihood of tumor and the claims are indefinite in being incomplete for omitting

essential steps, that is, the step of establishing the "corresponding reference" and "establishing a level of difference that is indicative of a like likelihood of tumor, such omission amounting to a gap between the steps and the omission of a critical element. See MPEP § 706.03(f).

Claims 1, 5, 12, 16-22, 28-30, 32-34, 36-39 are indefinite because neither claim 1 nor claim 36 contains a positive process step which clearly relates back to the preamble.

Claim 28 is indefinite in the recitation of "at least a 50% higher risk of death". Higher than what? The metes and bounds of the patent protection claimed are unclear.

19. No claims allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar
Primary Patent Examiner
September 21, 2006